which differ only in the technique of adsorption. Both represent combinations of toxoids prepared from organisms grown in Mueller-type media, *Bordetella pertussis* grown on solid charcoal agar medium without blood substances. The toxins are detoxified with formaldehyde and concentrated by alcohol fractionation (Pillemer method). Each dose (0.5 mL) contains 10 Lf diphtheria toxoid, 5.33 Lf tetanus toxoid, and 15 opacity units of pertussis vaccine. The preservative is 1:10,000 thimerosal.

The pertussis component includes 4 strains of *Bordetella pertussis* which are bulk standardized at 90 opacity units.

The refined toxoids are adsorbed on either aluminum phosphate (0.23 mg aluminum) or potassium alum (0.14 mg aluminum).

2. *Labeling*—a. *Recommended use/indications.* The package circular recommends these preparations for routine immunization of infants and children, 8 weeks to 6 years of age, against diphtheria, pertussis, and tetanus. Three 0.5 cc intramuscular injections at intervals of 4 to 6 weeks are recommended for primary immunization with a reinforcing injection about 12 months after the third dose. A booster dose of 0.5 cc is recommended at 4 to 6 years of age.

b. *Contraindications.* Convulsions following an earlier injection contraindicates further administration of vaccines containing pertussis. The product is not recommended for use in children over 6 years of age. The label recommends deferral of elective injections in the following situations: acute respiratory disease, or other active infection, during treatment with immunosuppressive agents, outbreaks of poliomyelitis in the community. Fractional doses are recommended in infants with cerebral injury, asthma, a strong family history of allergy, somnolence, or fever of greater than 102°F with an earlier dose.

3. *Analysis*—a. *Efficacy*—(1) *Animal.* This product meets Federal requirements.

(2) *Human.* A review of the literature did not reveal any studies which included a Dow (Pitman-Moore) DTP in a trial of prophylactic efficacy.

Immunogenicity to each component is reported. With regards to the pertussis component, Bordt reports (Ref. 2):

Age group	No. subjects	No. with titer <1:4 prevaccine	Percent conversion† <1:4 to >1:32 (0.1 mL)
<6 months	20	19	74
6 mos. to 2 yrs.	38	35	94
2 yrs. to 6 yrs.	37	32	94

The question as to whether 74 percent conversion in infants less than 6 months of age is adequate cannot be answered from the available data.

b. *Safety*—(1) *Animal.* This product meets Federal requirements.

(2) *Human.* In the report by Conner and Speers (Ref. 3), 220 injections were given to children aged 2 months to 5 years and reactions followed. Two whole cell DTP vaccines were used; one was this product. The proportion of children who received this product is not stated. Reactions were observed in 43.6 percent of recipients; none were encepholopathic, and no febrile convulsions were seen. Local reactions (inflamation or nodule formation at injection site in 29.6 percent) and systemic reactions (30.9 percent) occurred frequently.

4. *Benefit/risk ratio.* The benefit-to-risk assessment of this product is satisfactory for the aluminum phosphate product, would be satisfactory for the potassium alum product if it is shown to be effective for primary immunization, and is satisfactory for the potassium alum product when used for booster immunization.

5. *Critique.* Inasmuch as there are two products in terms of the "adsorbant" component, the Panel considered each independently, although both carry the same brand name.

The submission and supporting data provide satisfactory evidence or safety and immunogenicity for the aluminum phosphate product when used for primary immunization of infants and children.

In contrast, data were not submitted or available to provide satisfactory evidence for the immunogenicity of the potassium alum preparation.

6. *Recommendations.* The Panel recommends that this product, when prepared with aluminum phosphate, be placed in Category I and that the appropriate license(s) be continued with the stipulation that the labeling be revised in accordance with currently accepted guidelines and the recommendations of this Report.

The Panel recommends that this product, when prepared with potassium alum, be placed in Category I as regards its use for booster immunization, and that the appropriate license(s) be continued with the stipulation that the labeling be revised in accordance with currently accepted guidelines and the recommendations of this Report.

The Panel recommends that this product, when prepared with potassium alum, be placed in Category IIIA for primary immunization and that the appropriate license be continued for a period not to exceed 3 years during which time the manufacturer shall develop data regarding the efficacy of the product when sued for primary immunization. Labeling revisions in accordance with this Report are recommended.

Diphtheria and Tetanus Toxoids and Pertussis Vaccine Adsorbed Manufactured by Eli Lilly and Company

1. *Description.* This product is an alum-precipitated preparation of purified diphtheria and tetanus toxoids (Pillemer method) and extracted pertussis antigen. Each total human dose (1.5 mL) contains 15 Lf tetanus toxoid, 50 Lf diphtheria toxoid, and 12 protective units of pertussis antigen. The preservative is 1:10,000 merthiolate.

The methods of preparing the toxoids are classical, but the method for preparting the extracted pertussis antigen is not given. It is stated that the procedure permits cellular debris to be discarded.

2. *Labeling*—a. *Recommended use/indications.* This product is recommended for simultaneous active immunization of children not over 6 years of age against diphtheria, tetanus, and pertussis.

b. *Contraindications.* Use in the presence of acute infections should be postponed. Personal or family history of central nervous system damage or convulsions is an indication to use fractional dosage of individual antigens or 1/10 the recommended dosage of DTP.

Postvaccinal neurologic disorders, such as convulsions or encephalopathy, are a contraindication to further use of pertussis antigen (note apparent contradiction to above recommendation on fractional doses). It is noted that corticosteroid may interfere with the immune response.

3. *Analysis*—a. *Efficacy*—(1) *Animal.* This product meets Federal requirements.

(2) *Human.* This particular product has never been subjected to a controlled clinical trial of its prophylactic efficacy. This is of particular concern because of the unique nature of the pertussis component. It does meet the requirements of the mouse potency test which has been correlated with human efficacy for whole-cell vaccines and Pilemer's purified pertussis antigen in the British Medical Research Council

Field Trials. The product has been shown to stimulate mouse protective antibodies (measured by incumbating serum with organisms, then injecting intracerebrally in mice) and agglutinating antibodies measured by a slide test (apparently not quantitated). The significance of the latter tests is unknown. (See Weihl (Ref. 4).) The toxoid components appeared to produce an adequate response.

b. *Safety*—(1) *Animal.* This product meets Federal requirements.

(2) *Human.* Two studies (Refs. 3 and 4) purport to show that this vaccine produced a lower incidence of local and systemic reactions than whole-cell vaccine. It is not clear if a single lot of "Extracted" DTP was employed and how many (and which manufacturer's) whole-cell DTP vaccines were involved in the comparison. This study may be a melange of the experience of the investigators who carried out separate evaluation (C. Weihl, H. D. Riley, and J. Lapin.)

This is an extensively used product. Data from the manufacturer's complaint files do not indicate an excessive number of complaints or the existence of a serious problem.

c. *Benefit/risk ratio.* Assuming that the vaccine is efficacious, the benefit-to-risk assessment would be satisfactory, but there is insufficient information to determine this for primary immunization. The benefit-to-risk assessment of this product when used for booster immunization is satisfactory.

d. *Labeling.* Although postvaccinal neurological disorders, including convulsions, are listed as contraindications to further use of the vaccine, the labeling goes on to recommend fractional dosage. This contradictory.

The reference to avoiding the use of the vaccine when polio is present in the community is outdated and should be deleted.

4. *Critique.* This is the only vaccine considered by the Panel which is not a whole-cell vaccine or differs substantially from the pertussis vaccines used in the British Medical Research Council Field Trials, which established the correlation of vaccine efficacy with potency assayed by the intracerebral mouse protection test. This particular type of fractionated pertusis antigen has never been subjected to a controlled field trial of prophylactic efficacy. In view of its widespread usage, this is a matter of some concern, especially since the feasibility of performing such a trial is extremely remote. While the mouse protection test provides a reasonable interim basis for assuming that the vaccine is likely to be efficacious, additional studies to provide a quantitative assessment of the agglutinin response are indicated to provide further assurance. This is especially indicated by the uniqueness of this product and the reasonably good relationship of agglutinin titers and vaccine efficacy established in the British Medical Research Council Field Trials. Unfortunately, data on agglutinin response furnished by the manufacturer are of a qualitative nature based on a rapid slide agglutination test.

In the matter of safety, the data gives the general impression that the vaccine containing extracted pertussis antigen in somewhat less reactive than whole-cell pertussis vaccine in terms of local and minor systemic reactions. There is not sufficient basis to assume that this vaccine is any more or less safe than whole-cell vaccines in terms of the very low risk of serious encephalopathic reactions which accompanies the use of pertussis vaccines.

5. *Recommendations.* The Panel recommends that this product be placed in Category I as regards its use for booster immunization and that the appropriate license(s) be continued with the stipulation that the labeling be revised in accordance with currently accepted guidelines and the recommendations of this Report.

Although meeting mouse protection test requirements, this particular type of fractionated vaccine has never been subjected to a controlled field trial of prophylactic effectiveness. Such field trials do not appear to be feasible in the near future because of the relative rarity of the disease and for other practical reasons previously discussed in this report. Serological data from agglutination tests, although indicative of an immune response, are not considered definitive evidence of protection. These factors led to a divided vote by the Panel. Therefore the Panel, by a split vote of three to two, recommends that this product be placed in Category I for primary immunization.

Diphtheria and Tetanus Toxoids and Pertussis Vaccine Adsorbed Manufactured by Lederle Laboratories Division, American Cyanamid Co.

1. *Description.* This product contains diphtheria and tetanus toxoids, adsorbed, combined with pertussis vaccine, and suspended in isotonic saline with 1: 10,000 thimerosal added as a preservative. The diphtheria toxin and the tetanus toxin are detoxified with formaldehyde, and refined by the Pillemer Alcohol Fractionation Method, adsorbed with aluminum phosphate. Phase I pertussis vaccine is prepared by growing the organism in modified Cohen-Wheeler Broth. A single 0.5 mL dose contains 12.5 Lf of diphtheria toxoid, 5 Lf of tetanus toxid, and no more than 16 opacity units of *Bordetella pertussis.* Aluminum phosphate is contained in the final product at a concentration not greater than 0.8 mg per mL.

2. *Labeling*—a. *Recommended use/indications.* The package circular recommends this preparation for the simultaneous primary immunization of infants and children under 6 years of age against diphtheria, tetanus, and whooping cough, and for booster innoculations for this age group. Four 0.5 cc doses given intramuscularly are recommended, 3 doses at 4- to 6-week intervals with the fourth dose approximately 1 year later. A booster dose of 0.5 cc is recommended at 4 to 6 years of age (preferably at time of school entrance).

b. *Contraindications.* This product is not recommended for use in children over 6 years of age, nor for use in adults at any time. An acute febrile illness is considered an indication to defer immunization. The labeling states that neurologic disorders in infants and children do not now appear to be a sufficient reason for withholding immunization. If an unusual neurological response to any given dose is observed, the physician is advised to proceed with caution using fractional doses of antigens or deferring immunization until the child is at least 1 year of age. Corticosteroids are mentioned as having an immunosuppressive effect, and it is suggested that a booster dose be given 1 month or more after such therapy is discontinued.

3. *Analysis*—a. *Efficacy*—(1) *Animal.* This product meets Federal requirements.

(2) *Human.* No specific data regarding human immunogenicity or efficacy are provided in the submission. A number of reprints of reviews are included, all of which attest to the general safety and efficacy of DTP preparation in humans.

b. *Safety*—(1) *Animal.* This product meets Federal requirements.

(2) *Human.* No specific data regarding human safety are presented. References are made to the general body of knowledge supporting the safety of DTP products, but none provide specific data regarding the Lederle DTP, adsorbed product (Ref. 4a).

The manufacturer's marketing experience is listed in general terms only. In the past 5 years a few million doses of this DTP have been distributed. During that time, 62 complaints were received by the producer, but these are not detailed. It is noted that the main

complaints have been pain on injection, local erythema, and febrile reactions in some instances including convulsions. No deaths are reported.

c. *Benefit/risk ratio.* The benefit-to-risk assessment of this product when used for primary immunization cannot be determined with certainty, owing to the lack of human data on immunogenicity. The benefit-to-risk assessment of this product when used for booster immunization is satisfactory.

4. *Critique.* The major problem apparent in a review of this product is the lack of satisfactory evidence for the immunogenicity of the diphtheria and tetanus components of this vaccine, when used in primary immunization.

The labeling is in general satisfactory, but should be revised and updated along the lines suggested by this Panel in the Generic Statement on Labeling.

5. *Recommendation.* The Panel recommends that this product be placed in Category I as regards its use for booster immunization and that the appropriate license(s) be continued with the stipulation that the labeling be revised in accordance with currently accepted guidelines and the recommendations of this Report.

The Panel recommends that this product be placed in Category IIIA for primary immunization and that the appropriate license be continued for a period not to exceed 3 years during which time the manufacturer shall develop data regarding the efficacy of this product when used for primary immunization. Labeling revisions in accordance with this Report are recommended.

Diphtheria and Tetanus Toxoids and Pertussis Vaccine Adsorbed Manufactured by Massachusetts Public Health Biologic Laboratories

1. *Description.* This product consists of 10 Lf of diphtheria toxoid, 7.5 Lf of tetanus toxoid, 10 opacity units of thimerosal-killed pertussis bacilli suspended in culture supernatant, 1.0± 0.35 mg of aluminum phosphate, and 1:10,000 thimerosal in each immunizing dose of 0.5 mL. The pertussis component consists of 4 protective units per dose.

The pertussis vaccine is prepared from the growth of multiple Phase I cultures on the casein hydrolysate medium of Cohen and Wheeler.

2. *Labeling*—a. *Recommended use/indications.* The preparation is recommended for primary immunization of infants and children up to the age of 6 years. It is recommended that immunization start at the age of 2 to 3 months of age. Three intramuscular injections of 0.5 mL are given at intervals of at least 4 to 6 weeks. The third injection should be followed approximately 1 year later by a fourth injection to complete the basic series.

Reimmunization is recommended (0.5 mL) at the age of 4 to 6 years.

Emergency booster doses are recommended on serious exposure to pertussis if a booster dose of DPT has not been given within the preceding year.

b. *Contraindications.* Any respiratory or other acute infection is reason for deferring injection. If marked or systemic reactions follow the first dose, subsequent doses should be decreased to 0.1 mL and repeated every 4 weeks. If the child to be immunized has central nervous system abnormalities, the initial and subsequent doses should not exceed 0.1 mL per injection.

The risk of encephalopathic symptoms is described, but the package insert does not specifically advise that no further pertussis vaccine shoud be given if such symptoms occur after the first injection.

3. *Analysis*—a. *Efficacy*—(1) *Animal.* This product meets Federal requirements.

(2) *Human.* McComb (Ref. 5) studied immune response in infants given 3 doses of Massachusetts Public Health Biologic Laboratories' DTP vaccine. Unfortunately no serological specimens were taken before immunization. More than 60 children were tested for diphtheria and tetanus antitoxin after immunization and all had titers in excess of 0.1 unit. Eighty-four percent of 38 children under 2 years of age and 61 percent of children over 2 years of age had pertussis agglutinin titers of 1:320 and over after immunization. Provenzano (Ref. 6) studied 66 infants age 3 to 28 months who were given 3 doses of Massachusetts Public Health Biologic Laboratories' DTP vaccine. The geometric mean titer 3 months after injection was 109 agglutination units. Infants given more than 3 doses, including some plain pertussis vaccine, had titers almost twice as high. Serological data from this study are presented in more detail by Levine (Ref. 7), including information on individual serological responses. (Eight of 48 children had no pertussis agglutinin after the recommended schedule; the log titers varied between 1.6 and 2.8.)

b. *Safety*—(1) *Animal.* This product meets Federal requirements.

(2) *Human.* In the study of McComb (Ref. 5), the rate of febrile reactions was less than 10 percent and that of irritability 7 to 13 percent. In the study of Provenzano (Ref. 6), the rates of reactions also appeared acceptable.

c. *Benefit/risk ratio.* The benefit-to-fisk assessment for this product is satisfactory.

d. *Labeling.* Labeling generally conforms to the Public Health Service Advisory Committee on Immunization Practices recommendations. The label should clearly state that should a child experience convulsions, shock, encephalopathy, or thrombocythemia following an injection of DTP, the child should receive no further pertussis vaccine, but subsequent immunizations should be given with DT only.

4. *Critique.* A multitude of published studies demonstrate the efficacy of this product. The package insert does not define the risk of giving additional pertussis vaccine to a child who has previously had a severe reaction to pertussis vaccine.

5. *Recommendations.* The Panel recommends that this product be placed in Category I and that the appropriate license(s) be continued because there is substantial evidence of safety and effectiveness for this product. Labeling should be revised in accordance with the recommendations of this Report.

Diphtheria and Tetanus Toxoids and Perstussis Vaccine Adsorbed Manufacturd by Merck Sharp & Dohme, Division of Merck & Co., Inc.

1. *Description.* This manufacturer maintains a single license for two preparations of diphtheria and tetanus toxoids and pertussis vaccine. The first, apparently the older of the two products, is prepared by precipitating all three antigens with alum prior to combination, and contains 25 Lf of diphtheria toxoid, 10 Lf of tetanus toxoid, and 12 opacity units of pertussis vaccine per 0.5 mL dose. The second product is prepared by combining diphtheria and tetanus toxoids, absorbed, onto aluminum phosphate, with pertussis vaccine. This preparation contains 15 Lf of diphtheria toxoid and 5 Lf of tetanus toxoid with 12 opacity units of pertussis vaccine per 0.5 mL dose. Each preparation contains 4 protective units of pertussis vaccine per dose.

2. *Labeling*—a. *Recommeded use/indications.* The recommendations for the use of these two preparations differ slightly from each other, but both are acceptable by the standards of current immunization advisory groups. For each, 0.5 mL intramuscular doses are recommended, beginning before 2 months of age and separated by at least 1 month. Reinforcing doses are recommended 1 year later and between 3 and 5 years of age.

b. *Contraindications.* It is recommended that further injections of the preparation not be given if a neurologic reaction to the vaccine

occurs. It is also recommended that elective immunization be deferred during an epidemic of poliomyelitis. The recommendations for the alum precipitated preparation are dated nearly 17 years ago and those for the aluminum phosphate adsorbed preparation nearly 14 years ago.

3. *Analysis*—a. *Efficacy*—(1) *Animal.* These products met Federal requirements when manufactured.

(2) *Human.* Data are not available.

b. *Safety*—(1) *Animal.* These products met Federal requirements when manufactured.

(2) *Human.* These products were marketed for nearly 12 years through 1964, during which time many million doses were distributed. There were 132 reports of reactions, none of which was said to be significant.

C. *Benefit/risk ratio.* The benefit-to-risk assessment cannot be determined in the absence of efficacy data in humans.

4. *Critique.* This combined diphtheria and tetanus toxoid and pertussis vaccine is apparently licensed in two forms, one of which is alum precipitated, and the other of which is aluminum phosphate adsorbed. Neither has been marketed since 1964. Efficacy data related to this product are not available.

5. *Recommendations.* The Panel recommends that these products be placed in Category IIIC and that the appropriate license be revoked for administrative reasons because these products are not marketed in the form for which licensed and consequently there are insufficient data on labeling, safety, and effectiveness.

Diphtheria and Tetanus Toxoids and Pertussis Vaccine Manufactured by Merrell-National Laboratories, Division of Richardson-Merrell, Inc.

1. *Description.* This trivalent fluid vaccine contains, per each 0.5 ML dose, 10 Lf of diphtheria toxoid, 2 Lf of tetanus toxoid, not more than 20 opacity units of pertussis vaccine, and 1:10,000 thimerosal as a preservative, suspended in isotonic saline. Each dose contains 4 protective units of pertussis vaccine.

2. *Labeling*—a. *Recommended use/indications.* This product is recommended for the active immunization of infants and young children against diphtheria, tetanus, and pertussis simultaneously. Three intramuscular doses of 0.5 mL each are recommeded at 4- to 6-week intervals beginning age 2 or 3 months with a reinforcing dose 1 year later. The manufacturer does not specify preference for the fluid or adsorbed product.

b. *Contraindications.* An acute illness is considered reasons to defer immunization with this product. It is also recommended that routine immunization with this product not be given if the child exhibits a personal or family history of central nervous system disease or convulsions. There is also a warning about immunization during an epidemic of poliomyelitis. The occurrence of any type of neurologic symptom or sign following the administration of this product is considered an absolute contraindication to further use.

3. *Analysis*—a. *Efficacy*—(1) *Animal.* This product meets Federal requirements.

(2) *Human.* No human efficacy data are available for this trivalent fluid vaccine.

b. *Safety*—(1) *Animal.* This product meets Federal requirements.

(2) *Human.* Six reports of adverse reactions, all of minor consequence, were received by the manufacturer during a 5-year period when many hundred thousands of dose of this vaccine were distributed.

c. *Benefit/risk ratio.* The risk from this product appears to be minor; in the absence of human efficacy data for primary immunization, the benefit-to-risk assessment cannot be determined with precision. The benefit-to-risk assessment of this product when used for booster immunization is satisfactory.

4. *Critique.* This combined fluid preparation for immunization against diphtheria, tetanus, and pertussis appears to meet Federal regulations for efficacy and safety in animals and appears to be safe for humans. However, data regarding its immunogenicity in man are not available.

5. *Recommendations.* The Panel recommends that this product be placed in Category I as regards its use for booster immunization and that the appropriate license(s) be continued with the stipulation that the labeling be revised in accordance with currently accepted guidelines and the recommendations of this Report.

The Panel recommends that this product be placed in Category IIIA for primary immunization and that the appropriate license be continued for a period not to exceed 3 years during which time the manufacturer shall develop data regarding the efficacy of this product. Labeling revisions in accordance with this Report are recommended.

Diphtheria and Tetanus Toxoids and Pertussis Vaccine Adsorbed Manufactured by Merrell-National Laboratories, Division of Richardson-Merrell, Inc.

1. *Description.* This trivalent product for immunization against diphtheria, tetanus, and pertussis contains, per each 0.5 mL dose, 6.5 Lf of diphtheria toxoid, 5 Lf of tetanus toxoid, and not more than 15 opacity units of pertussis vaccine, adsorbed, with aluminum potassium sulphate. Each dose contains 4 protective units of pertussis vaccine.

2. *Labeling*—a. *Recommended use/indications.* This product is recommended for the active immunization of infants and young children against diphtheria, tetanus, and pertussis simultaneously. Three doses of 0.5 mL each intramuscularly are recommend at 4- to 6-week intervals beginning at age 2 or 3 months with a reinforcing dose administered 1 year later.

b. *Contraindications.* An acute illness is considered reason to defer immunization with this product. It is also recommended that routine immunization with this product not be given if the children exhibits a personal or family history of central nervous system disease or convulsions. There is also a warning about immunization during an epidemic of poliomyelitis. The occurrence of any type of neurologic symptom or sign following the administration of this product is considered an absolute contraindication to further use.

3. *Analysis*—a. *Efficacy*—(1) *Animal.* This product meets Federal requirements.

2. *Human.* The efficacy of this product was satisfactorily established by a 1950 study (Ref. 8) in which 100 infants were immunized and subsequently evaluated for the presence of immunity to diptheria, tetantus, and pertussis. Serologic responses were measured in 20 to 25 children for each of the vaccine components; all children studied had satisfactory respones to primary immunization.

b. *Safety*—(1) *Animal.* This product meets Federal requirements.

(2) *Human.* In the 1950 study (Ref. 8) of 100 infants given more than 300 injections of this product, no serious systemic or local reaction was observed. During the 5 years, 1968 through 1972, many million doses of this preparation were marketed, during which time 47 adverse reactions were reported. Four of these were serious, including three deaths, one of which was ascribed to an

anaphylactic reaction. There was one case of encephalitis.

c. *Benefit/risk ratio.* The benefit-to-risk assessment of this product is satisfactory.

4. *Critique.* This is a widely used trivalent preparation for immunization of young infants and children against diphtheria, tetanus, and pertussis which appears to be associated with significant reactions very rarely and which has been shown to be efficacious in humans.

5. *Recommendations.* The Panel recommends that this product be placed in Category I and that the appropriate license(s) be continued because there is substantial evidence of safety and effectiveness for this product. Labeling revisions in accordance with this Report are recommended.

Diphtheria and Tetanus Toxoids and Pertussis Vaccine Manufactured by Parke, Davis & Co.

1. *Description.* This product consists of a saline suspension of 12 protective units of pertussis vaccine (in three 0.5 mL doses) together with 50 Lf of diphtheria toxoid and 5 Lf of tetanus toxoid per 0.5 mL dose in 0.9 percent saline solution with 0.01 percent thimerosal as a preservative. It is presumably derived from the same mixture of selected strains of *Bordetella pertussis* as are used in the monovalent fluid vaccine.

2. *Labeling*—a. *Recommended use/indications.* For immunization of infants against diphtheria, tetanus, and pertussis starting at age 6 weeks to 3 monhs, give three 0.5 mL doses intramuscularly 4 weeks apart with a reinforcing dose 1 year later and a booster at age 3 to 6 years, or as a precaution in the presence of actual or potential exposure. For wound boosters, the use of tetanus toxoid or tetanus diphtheria toxoid is preferred. (Mention of the possible use of this product for rapid immunization should be deleted.)

b. *Contraindications.* This product is contraindicated in the presence of thrombocytopenia. When a patient is on immunodepressant therapy immunization should be deferred.

3. *Analysis*—a. *Efficacy*—(1) *Animal.* This product meets Federal requirements.

(2) *Human.* No specific data are presented.

b. *Safety*—(1) *Animal.* This product meets Federal requirements.

(2) *Human.* Only market experience is cited which suggests no problem.

c. *Benefit/risk ratio.* The benefit-to-risk assessment appears to be satisfactory when used for booster immunization since this product is typical of a vaccine that has been widely and successfully used with no unusual incidence of reactions (but it should be noted that recent English studies suggest that reactions are fewer with the adsorbed vaccine). For primary immunization the risk appears to be low; data relating to the efficacy of this agent for primary immunization are not available and accordingly benefit-to-risk assessment cannot be established with precision.

4. *Critique.* This is a classical fluid DTP with no adverse data reported and a history of extensive marketing, but no quantitative data on reactions and limited data on marketing experience are provided. On the basis of official tests and general experience the product appears acceptable, provided human data on efficacy are furnished. The extremely high dose of diphtheria toxoid should be justified or modified.

5. *Recommendations.* The Panel recommends that this product be placed in Category I as regards its use for booster immunization and that the appropriate license(s) be continued with the stipulation that the labeling be revised in accordance with currently accepted guidelines and the recommendations of this Report.

The Panel recommends that this product be placed in Category IIIA for primary immunization and that the appropriate license be continued for a period not to exceed 3 years during which time the manufacturer shall develop data regarding the efficacy of this product. Labeling revisions in accordance with this Report are recommended.

Diphtheria and Tetanus Toxoids and Pertussis Vaccine Adsorbed Manufactured by Parke, Davis & Co.

1. *Description.* This product contains 4 protective units of pertussis vaccine, 15 Lf of diphtheria toxoid, and 5 Lf of tetanus toxoid per 0.5 mL dose. The antigens are adsorbed on aluminum phosphate in 0.9 percent saline solution. Thimerosal 0.01 percent is added as a preservative.

2. *Labeling*—a. *Recommended use/indications.* This product is presented as providing efficient, convenient, and rapid immunization against the three diseases in question. Immunization is started at 6 weeks to 3 months with 3 doses of 0.5 mL each given 4 to 6 weeks apart and a reinforcing dose 1 year later. All injections are intramuscular. A booster is recommended at age 3 to 6 years or in the presence of actual or potential exposure, if 1 year or more has elapsed after the last dose.

b. *Contraindications.* Not recommended for children over 6 years, and should be deferred in children receiving immunodepressants or having acute illness. There is no mention of thrombocytopenia or encephalopathy as problems or contraindications.

3. *Analysis*—a. *Efficacy*—(1) *Animal.* This product meets Federal requirements.

(2) *Human.* The data provided by the manufacturer for its quadrivalent DTP poliomyelitis vaccine show satisfactory immunogenicity when used for primary immunization. (See the review of the quadrivalent product.)

b. *Safety*—(1) *Animal.* This product meets Federal requirements.

(2) *Human.* This product appears to be somewhat more reactive than might be expected (see Table 4 and section VC2 of manufacturer's data submission (Ref. 9)) but yardstick for evaluation is not apparent. Reported reactions for market experience appear within reasonable limits.

c. *Benefit/risk ratio.* The benefit-to-risk assessment of this product is satisfactory.

4. *Critique.* This is a classical adsorbed DTP which has been widely used with little adverse experience reported. It is prepared by well-established methods, tested for laboratory potency by a well-validated method, and appears only slighty more reactive than the ideal preparation. It seems acceptable for release as safe and effective, although comparative reactive data would be desirable as would information on the significance of the strains used in the pertussis vaccine component.

5. *Recommendations.* The Panel recommends that this product be placed in Category I and that the appropriate license(s) be continued because there is substantial evidence of safety and effectiveness for this product. Labeling revisions in accordance with this Report are recommended.

Diphtheria and Tetanus Toxoids and Pertussis and Poliomyelitis Vaccines Adsorbed Manufactured by Parke, Davis & Co.

1. *Description.* This is a quadrivalent product containing per 0.5 mL dose 15 Lf of diphtheria toxoid, 5 Lf of tetanus toxoid, 12.5 opacity units of *Bordetella pertussis* suspension, and poliomyelitis vaccine, trivalent, antigenically equivalent to 1 mL of fluid poliomyelitis vaccine. The poliomyelitis component is prepared from Type 1, 2, and 3 poliovirus grown in monkey kidney tissue culture, and inactivated with formaldehyde and supplemental ultraviolet irradiation. Each dose further contains 32.5 mcg of protamine sulfate,